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TRANSMITTAL FORM

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Application Number	USP 4,911,932 (Appln. No. 06/700,165)
Filing Date	Issued: March 27, 1990 (Filed: Feb. 11, 1985)
First Named Inventor	Charles E. Clum
Art Unit	
Examiner Name	
Attorney Docket Number	054824-0006

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
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- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below):

1. Response to Order to Show Cause with Exhibits 1 to 5;
2. Return-Receipt Postcard

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Morgan, Lewis & Bockius LLP		
Signature			
Printed name	Gregory T. Lowen		
Date	September 8, 2008	Reg. No.	46,882

CERTIFICATE OF TRANSMISSION/MAILING

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PATENT
Attorney Docket **054824-0006**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: **Charles E. CLUM *et al.***
Patent No. **4,911,932**
Issued: **March 27, 1990**
Filed: **February 11, 1985**
For: **Skin Care Compositions**

Date: September 8, 2008

RESPONSE TO ORDER TO SHOW CAUSE

In response to the Order to Show Cause under 37 C.F.R. 1.750 mailed July 9, 2008, Applicants submit that the patent term extension for the above-referenced patent should not be denied, based at least on the arguments provided herein. Because this response is being filed within two months from the mailing date of the Order, Applicants submit that the response is timely filed.

Brief Summary of the Order to Show Cause:

A request for patent term extension (PTE) of U.S. Patent No. 4,911,932 ("the '932 patent"), the claims of which encompass the skin-care composition product Vusion® Ointment, was timely submitted to the Patent Office. A subsequent letter received from the Food and Drug Administration (FDA) regarding the request for extension indicated that two of the three active ingredients of Vusion® Ointment, namely miconazole nitrate and zinc oxide, had previously been reviewed under Section 505 of the Federal Food, Drug, and Cosmetic Act (FFDCA) and had previously been granted permission for commercial marketing or use, but that the third active ingredient, white petrolatum, had not previously been subject to a regulatory review under Section 505. In view of the impending expiration of the '932 patent during the PTE review period, two consecutive requests for interim extensions of time were filed with and subsequently approved by the Patent Office. An Order to Show Cause, mailed by the Patent Office on July 9, 2008, challenges the eligibility of the '932 patent for the following reason.

In the Order, the Patent Office indicates that the statutory language of 35 U.S.C. 156(f) requires that when patent term extension is requested for a drug product containing multiple active ingredients, the eligibility of the drug product for extension is based on an analysis of each of the active ingredients as opposed to an analysis of the drug product as a whole. The Federal Circuit case of *Arnold Partnership v. Dudas* (70 USPQ 2d 1311 (Fed. Cir. 2004)) is cited for its holding that extension of the term of a patent claiming a drug composition comprising active ingredients A and B requires that either A or B must not have been previously approved for marketing. Both the court and the Patent Office point to the language of 35 U.S.C 156(a)(5)(A) as the statutory basis for this holding. Regarding the eligibility of the '932 patent for patent term extension, the Patent Office indicates that in view of the assertion by the FDA that both miconazole nitrate and zinc oxide had previously been reviewed under Section 505 of the FFDCA and previously granted permission for commercial marketing or use, those two active ingredients of Vusion® Ointment cannot serve as the basis for compliance with the requirements of 35 U.S.C. 156(a)(5)(A). However, because the FDA was unable to produce any evidence that white petrolatum (*i.e.*, the third active ingredient of Vusion® Ointment) had previously been

reviewed under Section 505 of the FFDCA and subsequently granted permission for commercial marketing or use, white petrolatum could serve as the basis for compliance with the requirements of 35 U.S.C. 156(a)(5)(A). However, the Patent Office states that a further analysis of the claims of the '932 reveals that white petrolatum is not explicitly recited as an ingredient in any of the claimed skin care compositions. A decision by the Commissioner of Patents (*In re Alcon*, 13 USPQ2d 1115 (Comm'r Pat. 1989) is cited for its holding that 35 U.S.C. 156(a)(5)(A) requires that at least one active ingredient of a drug product, that had not been previously approved for commercial marketing or use must be claimed in a patent for that patent to be eligible for patent term extension.

Applying the *In re Alcon* rationale to the request for patent term extension of the '932 patent, the Patent Office concluded that even though white petrolatum is present as an active ingredient in Vusion® Ointment and, unlike the other active ingredients miconazole nitrate and zinc oxide, had not previously been approved for commercial marketing or use, it is not specifically recited in any of the claims of the '932 patent, thereby rendering the '932 patent ineligible for patent term extension.

The Applicant has been given two months from the mailing date of the Order to show why PTE for the '932 patent should not be denied based on the above-summarized assertions by the Patent Office.

Applicants' Arguments:

Applicants submit that the '932 patent is eligible for patent term extension for at least the following reasons:

1. **Previous Approvals Of Zinc Oxide As An Active Ingredient As Identified in the Order To Show Cause Are Not Sufficient Because They Were Not Approved for Efficacy**

The Order to Show Cause states that zinc oxide, *i.e.,* one of the active ingredients of Vusion® Ointment is not compliant with the requirements of 35 U.S.C. 156(a)(5)(A) because of its earlier approvals for commercial marketing or use.

Applicants submit that all of the drug products identified by the Patent Office in the Order to Show Cause as containing zinc oxide as an active ingredient received first approval for commercial marketing or use prior to the enactment date of the Drug Amendments of 1962 (also known as the Kefauver-Harris Amendments) to the FFDCA.[1] Accordingly, Applicants submit that these drug products were approved under a safety only evaluation standard that is inadequate and insufficient for proper drug evaluation and therefore cannot be relied upon by the Patent Office as evidence of a previous approval for commercial marketing or use under 35 U.S.C. 156(a)(5)(A). Applicants therefore submit that zinc oxide as an active ingredient in Vusion® Ointment is not precluded from serving as the basis for compliance with 35 U.S.C. 156(a)(5)(A), which would render the '932 patent eligible for patent term extension. Applicants are aware of the district court decision in *Westwood Pharmaceuticals, Inc. v. Quigg* that held that the enactment of the Drug Amendments of 1962 did not affect the determination of whether a drug product was approved for commercial marketing or use by the FDA prior to the enactment of the 1962 amendments was considered an approval within the meaning of Section 505 of the FFDCA as amended.[2] Applicants submit that if this almost 20-year old case, which Applicants believe to have been wrongly decided, were considered today, the court would have reached a different decision in view of the FDA's more recent indication of the criticality of efficacy when considering the approval of a drug for commercial marketing or use. Further, Applicants submit that this court decision is limited to a drug product containing a single active ingredient and is not applicable to Vusion® Ointment, in which the three active ingredients of zinc oxide, miconazole nitrate and white petrolatum function as a single entity as described in section 2 of this response.

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[1] The product "BY-NA-MID" is listed in the Order as having three separate approval dates: October 16, 1958; September 6, 1962; and September 4, 1963. Since the first two approval dates predate the enactment date of the Drug Amendments of 1962, it is likely that they do not include a consideration of efficacy. There is no indication in the Order that the 1963 approval included a consideration of efficacy.

[2] *Westwood Pharmaceuticals, Inc. v. Quigg*, 13 USPQ2d 2067 (D.D.C. 1989).

Eligibility of a U.S. patent for patent term extension is dependent on compliance with 35 U.S.C. 156, and in particular, 156(a)(5)(A), which requires that

> "(a) The term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended in accordance with this section from the original expiration date of the patent, which shall include any patent term adjustment granted under section 154(b), if -
>
> (1) the term of the patent has not expired before an application is submitted under subsection (d)(1) for its extension;
>
> (2) the term of the patent has never been extended under subsection (e)(1) of this section;
>
> (3) an application for extension is submitted by the owner of record of the patent or its agent and in accordance with the requirements of paragraphs (1) through (4) of subsection (d);
>
> (4) the product has been subject to a regulatory review period before its commercial marketing or use; and
>
> (5)
>
> (A) except as provided in subparagraph (B) or (C), the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred;..."

"Regulatory review period" as recited above is defined in 35 U.S.C. 156(g) as follows:

> "For purposes of this section, the term 'regulatory review period' has the following meanings:
>
> (1)
>
> (A) In the case of a product which is a new drug, antibiotic drug, or human biological product, the term means the period described in subparagraph (B) to which the limitation described in paragraph (6) applies.
>
> (B) The regulatory review period for a new drug, antibiotic drug, or human biological product is the sum of -

> (i) the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 became effective for the approved product and ending on the date an application was initially submitted for such drug product under section 351, 505, or 507, and
>
> (ii) the period beginning on the date the application was initially submitted for the approved product under section 351, subsection (b) of section 505, or section 507 and ending on the date such application was approved under such section."

Applicants submit that the prior approvals of the zinc-oxide containing products cited in the Order by the Patent Office should not be considered as the first commercial marketing or use of zinc oxide under U.S.C. 156(a)(5)(A) for the reason that the regulatory review of these products under Section 505 of the FFDCA prior to the Drug Amendments of 1962 proceeded under a safety only standard. Evaluations of drug products under this standard was subsequently determined by the FDA to be inadequate and insufficient for evaluating the suitability of products for potential administration to the public, such that new approvals of the products were required.

Prior to 1962, drugs were approved based on an evaluation of safety only (see **Exhibit 1** at page 187). Further, generic versions of such drugs could be approved with a simple "paper" new drug application (NDA), which lacked generated data and was based solely on published scientific or medical literature describing the active ingredients as safe. Largely in response to the discovery that the use of thalidomide (a sedative marketed to alleviate the symptoms associated with morning sickness) by pregnant women caused birth deformities in thousands of infants in western Europe, the FFDCA was amended on October 10, 1962 (Public Law 87-781) to add a proof-of-efficacy requirement to new drug approval (see **Exhibit 2**).

In underscoring the importance of the Drug Amendments of 1962, a FDA-generated document (see **Exhibit 3** at page 1) states the following:

> "The Drug Amendments of 1962, passed unanimously by Congress, tightened control over prescription drugs, new drugs, and investigational drugs. It was recognized that no drug is truly safe unless it is also effective, and effectiveness was required to be established prior to marketing – a milestone advance in medical history...In the years since

> 1962 literally thousands of prescription drug items have been taken off the U.S. market because they lacked evidence of safety and/or effectiveness..."

The above statement makes it clear that it is FDA policy to act against drugs that are determined to be ineffective. Under the FFDCA, drugs which are not demonstrated to be effective are not approved.

A 2006 FDA-generated Guidance for FDA Staff and Industry document (see **Exhibit 4** at pages 8-9) addresses how the Drug Amendments of 1962 affected drugs that were already approved for commercial use on the day of enactment of the legislation (*i.e.*, October 10, 1962):

> "Between 1938 and 1962, if a drug obtained approval, FDA considered drugs that were identical, related, or similar (IRS) to the approved drug to be covered by that approval, and allowed those IRS drugs to be marketed without independent approval. Many manufacturers also introduced drugs onto the market between 1938 and 1962 based on their own conclusion that the products were generally recognized as safe (GRAS) or based on an opinion from FDA that the products were not new drugs. Between 1938 and 1962, the Agency issued many such opinions, although all were formally revoked in 1968 (see 21 CFR 310.00)...
>
> In 1962, Congress amended the [Federal Food, Drug, and Cosmetic] Act to require that a new drug also be proven effective, as well as safe, to obtain FDA approval. This amendment also required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that FDA had approved as safe between 1938 and 1962 through the new drug approval process. FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962...FDA's administrative implementation of the NAS/NRC reports was called the Drug Efficacy Study Implementation (DESI)....
>
> Because the DESI products were covered by pre-approved (pre-1962) applications, the Agency concluded that, prior to removing products found not effective from the market, it would follow procedures in the Act and regulations that apply when an approved new drug application is withdrawn:

- All initial DESI determinations are published in the *Federal Register* and, if the drug is found to be less than fully effective, there is an opportunity for a hearing.

- The Agency considers the basis of any hearing request and either grants the hearing or denies the hearing on summary judgment and publishes its final determination in the *Federal Register*.

- If FDA's final determination classifies the drug as effective for its labeled indications, as required by the Act, FDA still requires approved applications for continued marketing of the drug and all drugs IRS to it – NDA supplements for those drugs with NDAs approved for safety, or new ANDAs or NDAs , as appropriate, for IRS drugs. DESI-effective drugs that do not obtain approval of the required supplement, ANDA, or NDA are subject to enforcement action.

- If FDA's final determination classifies the drug as ineffective, the drug and those IRS to it can no longer be marketed and are subject to enforcement action."

Applicants submit that the above provided FDA policy shows that the FDA is evaluating for effectiveness, drugs previously (*i.e.*, pre-1962) approved under a safety-only evaluation, and that if such a drug is determined to be ineffective, it will be removed from the market. This potential action by the FDA is clear evidence that a safety only evaluation of a drug product is deemed by the FDA to be inadequate and insufficient.

The same FDA-provided document also addresses a grandfather clause that accompanied the 1962 Drug Amendments, but Applicants submit that this clause would not apply to the zinc oxide-containing products listed in the Order as having obtained approved NDA's.[3]

A FDA-generated Questions and Answers document created October 17, 2003 (see **Exhibit 5** at page 3) indicates that "DESI" drugs (*i.e.*, drugs that were approved solely on the basis of their safety prior to 1962) "may continue to be marketed until administrative

3 The grandfather clause exempts a drug from the effectiveness requirements if its composition and labeling has not changed since 1962 and if, on the day before the 1962 Amendments became effective, it was (a) used or sold commercially in the United States, (b) not a new drug as defined by the Act at that time, and (c) not covered by an effective application. The Exhibit 4 document indicates that the FDA believes that there are very few drugs on the market that are actually entitled to grandfather status and that the clause has been construed very narrowly by the courts.

proceedings evaluating their effectiveness have been concluded, at which point continued marketing is only permitted if an NDA is approved for such drugs." Applicants submit that such a statement is a clear indication that the previous approvals under a safety only evaluation are not recognized as true approvals subject to a regulatory review as contemplated by the 1984 Amendments because they failed to take into account the effectiveness of each of the evaluated drug products. Drugs previously approved under a safety only evaluation are subject to a new regulatory review process with the submission of a new NDA.

Applicants submit that based on the above evidence provided by Exhibits 1-5, it is clear that the FDA views a regulatory review of a drug product based solely on safety as inadequate and unsuitable, to the point where drugs previously approved under a safety only evaluation will be removed from the market if efficacy has not subsequently been satisfactorily demonstrated. Accordingly, Applicants submit that any permission granted for the commercial marketing or use of a drug product after a regulatory review period that involved a safety only analysis cannot be treated as qualifying as a first approval under 156(a)(5)(A) because such a review is not consistent with Congress' determination that drugs should also be evaluated for efficacy to protect the public.

Therefore, Applicants submit that the Patent Office has not met its burden of showing that zinc oxide has previously been approved as an active ingredient for commercial marketing or use under a regulatory review standard deemed to be acceptable to the FDA.

2. Vusion® Ointment Functions as a Single Entity

Applicants submit that Vusion® Ointment represents a topical formulation of three active ingredients that function together as a single indivisible entity. As such, Applicants submit that for the purposes of 35 U.S.C.156, Vusion® Ointment should be treated as a single product rather than the combination of three separate active ingredients.

Applicants are well aware of the Patent Office ruling in the Symbicort case and the Federal Circuit holding in *Arnold Partnership v. Dudas*. However, in contrast to the Symbicort

case, Applicants are not relying on the observed synergism between the active ingredients as a means of claiming no previous commercial approval of the individual active ingredients. Rather, Applicants submit that the distinguishing factor between Vusion® Ointment and the budesonide + formoterol fumarate dihydrate combination of Symbicort or the hydrocodone + ibuprofen combination of Vicoprofen is that in the latter two cases, the active ingredients remain separate and distinct from each other. None of the four active ingredients in these cases is relied upon to provide a physical property that is critical to the functioning of the Symbicort or Vicoprofen drug products.

In the Symbicort case, the active components are combined in an inhalation formulation while in the Vicoprofen case, the active components are combined in a tablet. Both of these formulations provide active components combined with an inactive vehicle. In contrast, the white petrolatum component of Vusion® Ointment possesses a physical aspect, in addition to its active properties, that is required for the formation of a functional skin-care composition. More specifically, the white petrolatum is an active component that also serves as a medium in which the other active ingredients of miconazole nitrate and zinc oxide can be uniformly dispersed and also maintained in close proximity to the affected skin area for an extended period of time. In addition, the white petrolatum aids in preventing moisture loss (a problem with infants, especially premature infants) at the site of application and keeps the infant's irritated skin clean and comfortable by providing a physical barrier from air, urine, stools, irritating lotions or soaps and chaffing from clothing or diapers. In the absence of white petrolatum, Vusion® Ointment would not be effective for its intended purpose.

Further, in the Symbicort and *Arnold Partnership* cases, the individual active ingredients (*i.e.*, the budesonide and formoterol fumarate dihydrate; or the hydrocodone and ibuprofen) could in theory be administered in tandem without any significant impact on therapeutic efficacy. In contrast, the individual active ingredients present in Vusion® Ointment simply could not be administered in such a fashion because there is a physical interaction that occurs between the three active components that requires their simultaneous presence to effectively function as a skin care composition.

Accordingly, Applicants submit that Vusion® Ointment is unique compared to other drug

products considered by the Patent Office for patent term extension because Vusion® Ointment requires for its functioning a physical interaction between its three active components that merits its evaluation as a single indivisible entity. Since Vusion® Ointment as a single entity has not been previously approved under Section 505 of the FFDCA, Applicants submit that this fact can serve as the basis for compliance with 35 U.S.C. 156(a)(5)(A) and the basis for eligibility of U.S. Patent No. 4,911,932 for patent term extension.

3. White Petrolatum is Inherently Included in the Phrase "Skin Care Composition"

Applicants acknowledge that white petrolatum is not explicitly recited in the claims of U.S. Patent No. 4,911,932 but submit that it is inherently included in the recitation of claims 1-4 because of the phrase "skin care composition". Applicants submit that a skilled person would appreciate that a topical composition directed to skin care would require, in addition to the explicitly recited miconazole nitrate and zinc oxide, an additional component to serve as a means for effectively applying the miconazole nitrate and zinc oxide. The desirability of such a component is apparent from the teaching of U.S. Patent No. 4,911,932 that the skin care compositions of the invention could be "applied topically to prevent or treat acute inflammatory skin conditions, especially in young children" (col. 1, lines 12-15). The skin to be treated may be "sensitive and painful to the touch" and "chaffing" may occur (see col. 1, lines 16-28). Examples IV and V in the specification of U.S. Patent No. 4,911,932, reproduced below, which are represented as effective embodiments of the claimed skin care compositions, contain the active ingredients present in Vusion® Ointment.

EXAMPLE IV

An ointment skin care composition is prepared in accordance with the procedure of Example II and has the following formulation:

	% by w/w
white petrolatum	84.75
zinc oxide	15.00
miconazole nitrate	0.25
	100.00

EXAMPLE V

An ointment skin care composition is prepared in accordance with the procedure of Example II and has the following formulation:

	% wt/wt
white petrolatum	81.35
zinc oxide	15.00
Thixcin R (NL Chemical's tradename for trihydroxystearin)	3.00
miconazole nitrate	0.25
fragrance	0.40
	100.00

In addition, Applicants point out that the *in vivo* tests demonstrating the synergistic efficacy of the claimed skin care compositions were conducted on a combination of miconazole nitrate, zinc oxide and petrolatum (see col. 5, lines 13-17).

Based on the above information disclosed in U.S. Patent No. 4,911,932, Applicants submit that white petrolatum would be considered by a skilled person as an inherent component

in the claimed skin care composition comprising miconazole nitrate and zinc oxide. Since white petrolatum has not been previously approved under Section 505 of the FFDCA, Applicants submit that white petrolatum as an active ingredient in Vusion® Ointment can serve as the basis for compliance with 35 U.S.C. 156(a)(5)(A) and the basis for eligibility of U.S. Patent No. 4,911,932 for patent term extension.

4. The Three-Year New Product Marketing Exclusivity for Vusion® Ointment Expires February 16, 2009

The Order states that "should the USPTO deny the PTE for the '932 patent, where extension is sought based on the regulatory review period for VUSION®, the previous interim extensions granted pursuant to section 156(e)(2) would be vacated *ab initio*" (emphasis added). MPEP 2775.01, which is also cited by the Order, does not contain this definitive language regarding vacation of the earlier granted interim extensions. Rather, this section states that "where an interim extension has been granted and it is subsequently determined that the patent is not eligible for patent term extension, the interim extension may be vacated *ab initio* ..." (emphasis added). Applicants request clarification as to the reasons for the Order seemingly adopting a more stringent approach regarding vacation of the interim extensions that is suggested by the MPEP.

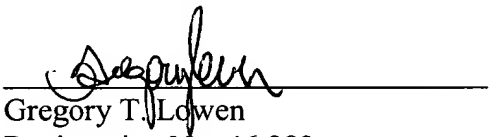
Further, Applicants point out that Vusion® Ointment is entitled to three years of new product marketing exclusivity until February 16, 2009 while the current interim extension is set to expire on March 27, 2009. If the Patent Office were to deny eligibility of the '932 patent for PTE, it is unclear to Applicants why they will apparently be denied an opportunity for further rebuttal in view of the absence of any impact on the public prior to February 16, 2009. Applicants submit that denial of their ability to further rebut a negative decision either to the Patent Office or through appeal to an appropriate court would cause irreparable harm to Applicants, given that removal of the interim extension would result in expiration of the '932 patent, loss of Orange Book listing for the '932 patent and possible loss of standing for purposes of appeal to a court.

For at least these reasons, Applicants request that the previously granted interim extension remain in place should the Patent Office find the arguments presented herein to be unpersuasive so as to provide Applicants with an opportunity for further rebuttal to the Patent Office and/or appeal to the appropriate court.

5. Conclusion

Applicants submit that based on at least the above-presented arguments, U.S. Patent No. 4,911, 932 should be eligible for patent term extension.

Respectfully submitted,
Morgan, Lewis & Bockius LLP



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Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process

GERALD J. MOSSINGHOFF*

I. INTRODUCTION

There is a paucity of legislative history on the Hatch-Waxman Act.[1] This article will try to provide a general overview of the legislative process and some insight into the Act's underlying assumptions, with the help of some graphics. With a bill as hard-fought as Hatch-Waxman, there was much written about it after the fact, but not a great deal of coherent legislative history. The article also provides a timetable to compare the drug discovery and development, patent protection, and generic competition processes that the Act affects.

Prior to 1962, drugs were approved for safety only. Senator Estes Kefauver (D-TN) tried for years to add an efficacy requirement, a concept that the research-based industry fully supported, but as often happens in Washington, there was a logical disconnect. The Thalidomide problem in infants — involving safety — resulted in the 1962 drug amendments[2] to the Federal Food, Drug, and Cosmetic Act,[3] which added a proof-of-efficacy requirement to new drug approval. Thus, new drugs must be proven safe and effective prior to the Food and Drug Administration's (FDA's) approval. Also, for drugs approved prior to 1962, generic versions could be approved with a "paper" new drug application (NDA). The paper NDA was based solely on published scientific or medical literature; a generic manufacturer could get its drug approved by showing that learned articles had been written about the chemical demonstrating that it was safe. After 1962, there was congressional testimony that there were 150 drugs that were off-patent, but for which there were no generics because generic companies simply would not spend the time and money doing the clinical trials to get to market, and that there were only fifteen "paper NDAs," for post-1962 generics.[4]

For those who ask whether Hatch-Waxman was a good deal or a bad deal for the research-based pharmaceutical industry, the most learned response is: It was not a good deal, unless one believed that FDA was going to go forward with its plans to implement abbreviated new drug applications (ANDAs) through regulation. If one thought that was going to happen — and FDA was working on it — then Hatch-Waxman probably was a good balance. If one did not think that would ever happen, Hatch-Waxman probably was not a good balance, at least at the time.

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* Mr. Mossinghoff is Senior Counsel to the law firm of Oblon, Spivak, McClelland, Maier & Neustadt, P.C., Arlington, VA. Mr. Mossinghoff is a former Commissioner of Patents and Trademarks, U.S. Patent and Trademark Office, U.S. Department of Commerce, and a former President of the Pharmaceutical Manufacturers Association (predecessor organization of the Pharmaceutical Researchers and Manufacturers of America).

[1] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified at 15 U.S.C. §§ 68b-68c, 70b (1994); 21 U.S.C. §§ 301 note, 355, 360cc (1994); 28 U.S.C. § 2201 (1994); 35 U.S.C. §§ 156, 271, 282 (1994)).

[2] Pub. L. No. 87-781, 76 Stat. 780 (codified at 21 U.S.C. §§ 321, 331-32, 348, 351-53, 355, 357-60, 372, 374, 376, 381).

[3] Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended 21 U.S.C. §§ 301 et seq.).

[4] H.R. REP. No. 98-857, pt. 1 (1984); *see also* Gilston, *The Generic Patent Compromise*, MED. ADVERTISING NEWS, Apr. 30, 1984, at 16-17.

II. DRAFTING THE HATCH-WAXMAN ACT

The plan for patent term restoration had its beginnings in President Carter's Administration. In 1978 President Carter launched a major domestic policy review on industrial innovation and that team recommended patent term restoration for pharmaceuticals and any other product that required regulatory review — to compensate for, or restore to the term of the patents, the time lost in regulatory review. President Reagan's Cabinet Council on Commerce and Trade also supported the proposal. Indeed, the Reagan Administration's first-term use of Cabinet Councils was a very orderly management and policymaking process. Then-Secretary of Commerce Malcolm Baldridge set up an intellectual property committee under the Cabinet Council on Commerce and Trade; chaired by the author, the committee was set at the Assistant Secretary level, including Bill Baxter of the Antitrust Division at the U.S. Department of Justice. The committee recommended, and the Cabinet Council supported, patent term restoration. That recommendation turned into a bill — S. 255 —[5] that passed the Senate and was referred to the House of Representatives. In the House, the bill's supporters put it on the suspension calendar, which requires a majority of two-thirds to suspend all the rules and enact the bill.[6] If a bill fails to get a two-thirds majority, then it must go back to the House Rules Committee and go through the regular committee process. S. 255 failed. Although it received a simple majority of the votes, it failed to pass the House by the necessary two-thirds majority on the suspension calendar. The vote, however, served as a wake-up call for generic drug manufacturers. Congressman Henry A. Waxman (D-CA), one of the most effective in the House of Representatives and then-Chairman of the Health Subcommittee, took on the issue. Suddenly, what had been a patent term restoration bill became a patent term restoration and drug price competition bill, and a whole new title was added that complicated the bill even further.

Finally, Public Law 98-417 (the Hatch-Waxman Act) was enacted in 1984. There have been several other developments in Hatch-Waxman's history, although these are not nearly as significant as the bill's enactment. First, animal drugs were added with the 1988 Generic Animal Drug and Patent Term Extension Act,[7] where generic animal drugs were added to the mix with an identical statutory template. The Uruguay Round Agreements Act[8] provided for what was called the "Delta Period." That Act provided that any drug with a patent in effect on June 8, 1995, or any patent application pending at that time would get the term of twenty years from the time of filing or seventeen years from the time of grant, whichever was longer. The difference between those two dates was referred to as the "Delta Period." In effect, the Act created a compulsory licensing provision during the delta period. If someone had invested significant amounts of money to get ready to come on the market during the Delta Period, the owner of the patent could not get an injunction, but would be entitled to receive only "equitable remuneration." The "equitable remuneration" term came out of the actual negotiations for the Agreement on Trade-Related Aspects of Intellectual Property Rights.[9] The issue was immediately raised: During this Delta Period, could

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[5] S. 255, 98th Cong., 2d Sess. (1984).

[6] CHARLES W. JOHNSON, HOW OUR LAWS ARE MADE, S. DOC. NO. 105-14, at 20 et seq. (1997).

[7] Pub. L. No. 100-670, 102 Stat. 3971 (1988) (codified at 21 U.S.C. §§ 301 note, 360b, 360b notes, 321, 353; 28 U.S.C. § 2201; 35 U.S.C. §§ 156, 271).

[8] Pub. L. No. 103-465, 108 Stat. 4809 (1994) (codified at 19 U.S.C. §§ 2252 et seq. (1994)).

[9] Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, LEGAL INSTRUMENTS — RESULTS OF THE URUGUAY ROUND vol. 31; 33 I.L.M. 81 (1994).

an ANDA be approved to permit a generic to come to the market? The issue was determined authoritatively in 1995 — and the answer was "no" — by the U.S. Court of Appeals for the Federal Circuit in *Bristol-Myers Squibb v. Royce*.[10] The court held that, during the Delta Period, a generic drug company could not bring a drug to market under the ANDA route. A generic company could bring a drug to market if it did all the clinical trials, but if it did not do the trials and wanted to go the ANDA route, the drug could not come on the market during the Delta Period.[11] Senators David Pryor (D-AR) and John Chafee (R-RI) tried to change that ruling through legislation, and it became a major issue. The research-based industry sought a resolution in which anybody could come onto the market during the Delta Period, but if one wanted to use the Hatch-Waxman shortcut, one had to use the whole Hatch-Waxman process. It is no longer a major issue but to several companies it was a significant financial development.

Another key development was the case of *Merck v. Kessler*,[12] the defendant parties of which were David Kessler, then-Commissioner of Food and Drugs, and Bruce Lehman, Commissioner of Patents and Trademarks. This case involved the issue of whether a patent holder can take twenty years from time of filing or seventeen years from time of grant, whichever is longer, and add it to the Hatch-Waxman extension. Originally, the U.S. Patent and Trademark Office (PTO) decided that patent holders could not; they could add the Hatch-Waxman extension to the seventeen-year period from time of grant, and not to the additional Delta Period. The Court of Appeals for the Federal Circuit reversed that PTO determination, although it did sustain it for the patents on five drugs that were still in force *only* because of Hatch-Waxman. The court ruled that, because the patents had not expired only by reason of Hatch-Waxman extensions, they did not get the benefit of the Delta Period.

III. A LOOK AT HATCH-WAXMAN

Title I of the Act contains the drug price competition part, specifically authorizing ANDAs and specifically prohibiting FDA from doing more than asking for bioavailability studies. In that regard, it is a unique piece of legislation because it actually ties the hands of a regulatory agency — in the area of public health — by providing specifically that FDA can require only bioavailability studies for ANDAs.[13] There is a five-year data exclusivity for new molecular entities (NMEs). The Act provides for a period of exclusivity such that once an NME is approved, a generic version cannot be approved for five years. That generally is referred to as "data exclusivity." The Act also calls for a three-year data exclusivity period for supplements requiring clinical trials. One of four certifications must be made when someone files an ANDA: 1) that the drug has not been patented; 2) that the patent has already expired; 3) the date on which the patent will expire, and that the generic drug will not go on the market until that date passes; and 4) that the patent is not infringed or is invalid. Those certifications are now referred to as the paragraphs I, II, III, and IV certifications.

A major issue during the pendency of the Hatch-Waxman legislation involved paragraph IV certifications. If a generic company said the patent was invalid or not

[10] 69 F.3d 1130 (Fed. Cir. 1995). Also, the *Bristol-Myers* opinion provides a good summary of the key provisions of the Hatch-Waxman Act.

[11] *Id.* at 1137.

[12] 80 F.3d 1543 (Fed. Cir. 1996).

[13] H.R. REP. No. 98-857, pt. 1, at 72 (1984).

infringed, how long would FDA be required to wait before approving the generics for marketing? For much of the debate, that period was eighteen months, however, through the work of the research industry, that time period was changed to thirty months. Thus, there is a thirty-month litigation, or cooling-off period such that once a generic determines that the patent is invalid or not infringed, it has to notify the patent owner, who has forty-five days in which to file an infringement action and then another thirty months of exclusivity before an ANDA can be approved (unless there is a final appellate decision earlier, which is highly unusual).

The patent term restoration part of the Act generally appears in title 35 of the *United States Code*. These are very long, very complicated provisions. For the patent term restoration period, a pioneer receives an extension term equal to one-half of the time of the investigational new drug (IND) period — running from the time in which a pioneer can begin human clinical trials — plus the NDA period — the period during the NDA review.[14] The maximum extension is five years and the total market exclusivity time cannot exceed fourteen years. The length of the exclusivity periods are strictly arbitrary legislative numbers pulled out of the air. Pipeline drugs — drug applications pending at the time the Act was passed — received two years or less of exclusivity on the assumption that if they were in a pipeline already, they would be approved in a year or two, so there was no need to give them more. Some pipeline drugs, however, have taken eight years for approval.

Finally, there is a provision that the pioneer must exercise due diligence in order to achieve patent term restoration, or a period of lack of diligence will be subtracted from the equation; that provision has never been used. The famous case of *Roche Products v. Bolar Pharmaceuticals*[15] was reversed specifically in section 271(e)(1) of title 35 of the *United States Code*. The result is that the day after the patent expires, generics are being served and dispensed to patients. Thus, the day after the patent is ineffective or expired, generic competition comes onto the shelves in the pharmacies ready to be dispensed to patients.

Another patent issue is constructive infringement. A constructive infringement is a fictional infringement, which in effect states that filing an ANDA and informing FDA under paragraph IV that the patent is either invalid or not infringed amounts to a patent infringement in and of itself.[16] Then all the other provisions of title 35 and title 28 of the *United States Code* come to bear, and a patent holder can file a regular infringement action against the generic company in a federal district court. The Act specifies that each patent can be extended only once, but the extended patent does cover subsequently approved uses for the period of the extension.

A number of assumptions were made in enacting Hatch-Waxman. One major assumption underlying the Hatch-Waxman Act was that duplicates of pioneer drugs would be the same as the innovator's drug. FDA still uses the plus-or-minus-twenty-percent test to determine blood serum bioavailability (i.e., the amount of active ingredient in the blood over a period of time has to come within plus-or-minus twenty percent of that which is observed when the innovator's drug is ingested). Twenty percent is a fairly good margin, and many medical professionals believe that for drugs that have a wide index of tolerance, twenty percent is not important at all; in such instances, twice as much or half as much of the active ingredient in a generic product will still work. For drugs where there is a very narrow therapeutic band, for example, where a patient gets antiseizure medication, plus-or-minus twenty percent may not be

[14] 35 U.S.C. § 156.

[15] 733 F.2d 858 (Fed. Cir. 1984).

[16] *See* 35 U.S.C. § 271(e)(2).

appropriate. This is true particularly if a drug is at that higher end of bioavailability and a patient is titrated on the higher end (plus twenty percent) and then a second generic is dispensed where the active ingredient was at the lower end (minus twenty percent); mathematically, that is a fifty percent swing and may not be safe or effective. It is a curious thing that FDA has not altered its regulatory approach to this situation. With the advances in modern pharmaceutics, those standards could be tightened. Although such tightening might not be to the advantage of the brand name companies, it could be to the advantage of patients.

A second assumption was that bioequivalence data was an effective surrogate for safety and efficacy — that products approved pursuant to ANDAs would meet the same regulatory requirements as pioneers. That was a good assumption, but there was always a feeling on the part of the research-based industry that, in FDA's view, pioneers wore the "black hats" and generics wore the "white hats," and review and approval were slightly relaxed. In fact, Joseph Stetler co-authored a book about the "generic scandal," when procedures got very relaxed during that period of time.[17] ANDA applicants need not meet additional requirements, but there remains a specific provision that bioavailability is the only test FDA can require.

Another assumption was that pipeline drugs would be approved shortly after the Act's enactment, and that two-year extensions were adequate. In one famous case, the drug was not approved for eight years.[18] Two key assumptions were that five years of extension and fourteen years of market exclusivity were sufficient to stimulate research and development — again, numbers pulled out of the air. The reasoning used in determining the patent term restoration part of the Act was, "If a mousetrap gets seventeen years of protection, why not a new life-saving drug?" If a mousetrap gets seventeen years or twenty years from time of filing, why would a brand-name research-based drug be limited only to fourteen years?

Another assumption underlying Hatch-Waxman was that development of generic products prior to patent expiration would have minimal effects on pioneer products. In practice, however, many generics have impacted pioneer sales quickly. Three months after Naprosene® went off-patent, its manufacturer, Syntax, lost seventy-five percent of its market to the generic product.

Another assumption was that it was not necessary to increase incentives for pioneers to develop second uses for patented products. There appears to be little basis for this assumption, and the Act actually removes incentives for finding new uses for patented drugs. In fact, there are many cases where it is a good idea to be able to extend the same patent for a new NME or a new use of an approved NME.

IV. POTENTIAL HATCH-WAXMAN REVISIONS

There are several key potential revisions that were identified in the Boston Consulting Group study in 1996.[19] Two of the Hatch-Waxman revisions mentioned include a one-for-one extension, and a change from the one-half of IND period to a full IND. Medical reviewers change as people come through FDA, and each reviewer makes a new contribution to the approval process. The reviewers ask questions regarding drugs that are brand new, perhaps, or have new pharmacological activity, but

[17] C. JOSEPH STETLER & WILLIAM C. CRAY, PATIENTS IN PERIL? THE STUNNING GENERIC DRUG SCANDAL (1991).

[18] Gerald J. Mossinghoff, *Independent Patent Review for "Pipeline" Drugs Would Advance Intellectual Property Rights*, 13 LEGAL BACKGROUNDER (Washington Legal Found. Aug. 7, 1998).

[19] THE BOSTON CONSULTING GROUP, SUSTAINING INNOVATION IN U.S. PHARMACEUTICALS, INTELLECTUAL PROPERTY PROTECTION & THE ROLE OF PATENTS (Jan. 1996).

nobody ever goes back and "unasks" the old questions. FDA reform legislation[20] was enacted because of the concern that overall drug development time was getting longer and longer. FDA has done a remarkably good job in cutting back the time for NDA review, but human clinical trials take a long time to conduct before that review; indeed, clinical trial testing time actually is getting longer.

Removing the two-year limit for pipeline drugs and the arbitrary five- and fourteen-year limitations is another proposal put forward. The revision also would permit multiple extensions of the same patent and then change the five-year data exclusivity to ten years in accordance with international standards, such as those in Europe and Japan. Why should foreign patent holders have ten-year data exclusivity while U.S. patent holders only have five?

V. NEW MEDICINES TIMETABLE

The new medicines timetable, above, illustrates pioneer drug development, patent activity, and generic competition activity. It illustrates a textbook case, as there probably is no drug in existence that follows this timetable exactly. The timetable does, however, permit a realistic basis on which the afternoon interactive workshop discussion is focused. It shows drug discovery in the early stages and the major milestones — when the drug IND is approved, when the drug enters human clinical trials, and so forth. The timeline tracks the progress from Phases I, II, and III through the acceptance of the NDA at FDA. A lot of time and thought go into the preparation of an NDA (although the review time is decreasing) before it is approved. The timeline also provides a general idea of when resources are committed on the generic side and the steps that need to be taken before there is an expiration of the patent, and the generic can be marketed.

Discovery is a continuing process, not a single point in time. Preclinical testing, i.e., laboratory and animal testing, occurs later. Sometime during that preclinical testing, but well in advance of the IND filing, the U.S. patent application is filed. Foreign patent applications must be filed within one year if the patent holder is under the Paris Convention[21] and a slightly longer period under the Patent Cooperation Treaty,[22] which most of the industry uses.

At some point the IND is approved by FDA — either it is approved pro-actively or a thirty-day period goes by without a hold. Then begins the very expensive Phase I, II, and III studies following the IND approval. At some point, FDA accepts an NDA (although in practice companies do some negotiating and discussing with FDA before they file the NDA). From IND approval through FDA acceptance is what is referred to as the IND period. Patent holders receive a restoration of one-half of the IND period. FDA then reviews the NDA in about fifteen or sixteen months. When the agency approves the drug, it may then be marketed.

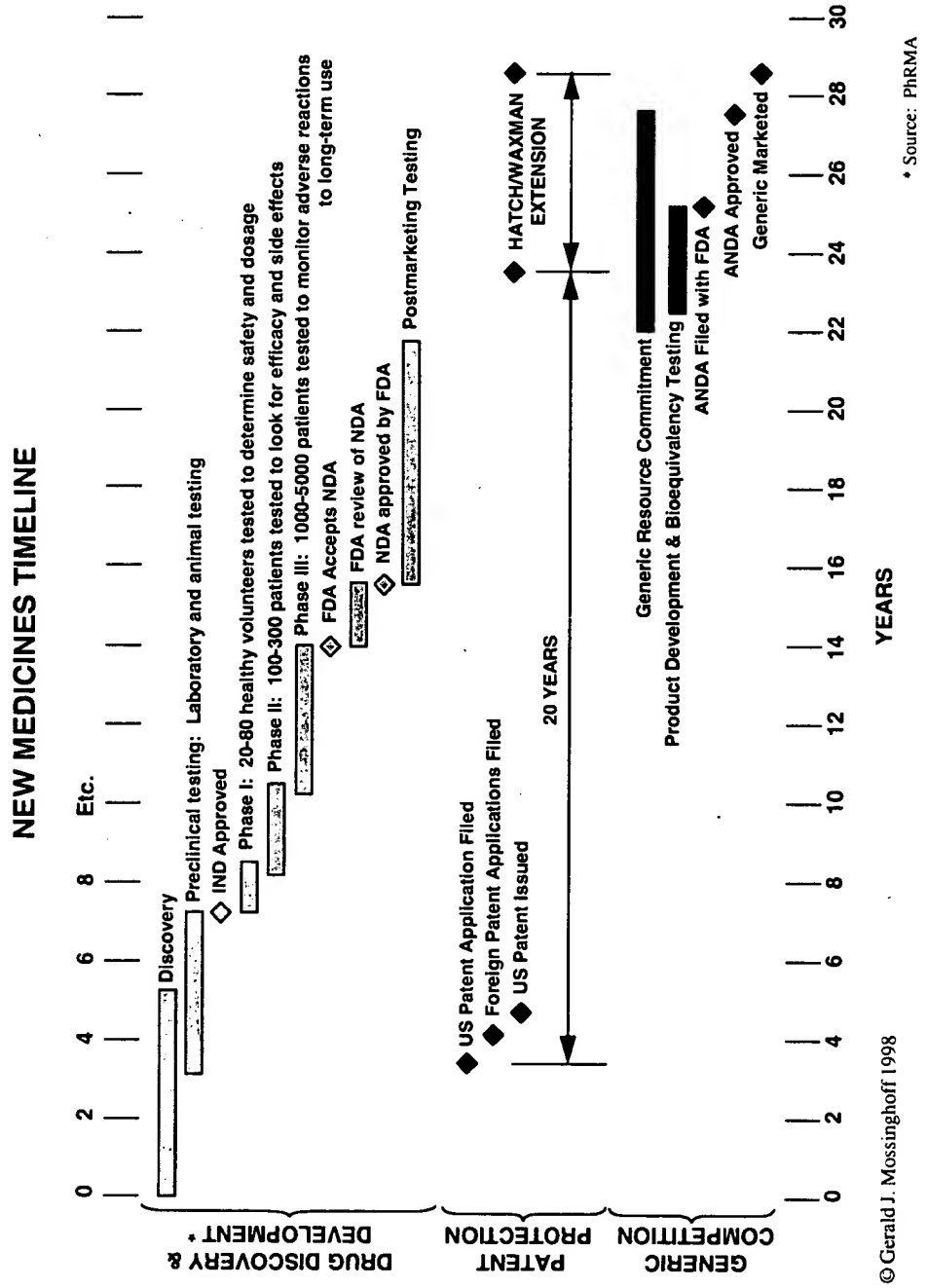
The U.S. patent, however, has been issued long before clinical trials begin. When the Hatch-Waxman formula operates, the twenty-year patent term is measured from the time of filing the drug application, so the twenty-year period is extended. Postmarket testing (Phase IV) is a continuous thing, so it has been left open-ended. The extension will fall exactly within the five-year limitation and the time from drug approval (roughly sixteen years) to the time the patent expires (twenty-eight years), still falling within the fourteen-year cap of the Hatch-Waxman Act.

[20] Food and Drug Administration Modernization Act, Pub. L. No. 105-115, 111 Stat. 2296 (1997).

[21] *Reprinted in* SELECTED INTELLECTUAL PROPERTY & UNFAIR COMPETITION STATUTES, REGULATIONS & TREATIES 805 (Roger E. Schecter ed. 1997).

[22] *Id.* at 700.

This timeline is an idealized view of the development process regarding the time frames and the regulatory procedures. At some point prior to the expiration of the original patent, however, generic resources are committed. A key issue in the area is product bioequivalency testing under paragraph III. The chart is not big enough to accommodate a paragraph IV certification with a litigation timeline, so this timeline uses a paragraph III ANDA filing. The ANDA is approved in the timetable in over two years. Generic marketing occurs on the day that the patent expires after having been extended.



VI. CONCLUSION

The Hatch-Waxman Act is significant to the U.S. healthcare system in many important respects. The robust generic drug industry owes its very existence to the Act, and patent term extensions or restorations are very important to the research-based pharmaceutical industry. But many of the assumptions made fifteen years ago when this Act was passed — which provided the bases for the arbitrary time limits established in the Act — have proven to be invalid, as pointed out in the Boston Consulting Group study.[23] Thus, it is time to revisit the Hatch-Waxman Act with a view to increase the patent incentives for the creation of new life-saving medicines.

[23] *See supra* note 19.

Federal Food, Drug, and Cosmetic Act

APPENDIX

- Section 107(c) of Drug Amendments of 1962
- Public Law 88-136; Revolving Fund
- Section 108 of Animal Drug Amendments of 1968
- Section 5 of Orphan Drug Act

SECTION 107(c) OF DRUG AMENDMENTS OF 1962 1

(c)(1) As used in this subsection the term "enactment date" means the date of enactment of this Act; and the term "basic Act" means the Federal Food, Drug, and Cosmetic Act.

(2) An application filed pursuant to section 505(b) of the basic Act which was "effective" within the meaning of that Act on the day immediately preceding the enactment date shall be deemed, as of the enactment date, to be an application "approved" by the Secretary within the meaning of the basic Act as amended by this Act.

(3) In the case of any drug with respect to which an application filed under section 505(b) of the basic Act is deemed to be an approved application on the enactment date by virtue of paragraph (2) of this subsection—

(A) the amendments made by this Act to section 201(p), and to subsections (b) and (d) of section 505, of the basic Act, insofar as such amendments relate to the effectiveness of drugs, shall not, so long as approval of such application is not withdrawn or suspended pursuant to section 505(e) of that Act, apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application, but shall apply to any changed use, or conditions of use, prescribed, recommended, or suggested in its labeling, including such conditions of use as are the subject of an amendment or supplement to such application pending on, or filed after, the enactment date; and

(B) clause (3) of the first sentence of section 505(e) of the basic Act, as amended by this Act, shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling covered by such approved application (except with respect to such use, or conditions of use, as are the subject of an amendment or supplement to such approved application, which amendment or supplement has been approved after the enactment date under section 505 of the basic Act as amended by this Act) until whichever of the following first occurs: (i) the expiration of the two-year period beginning with the enactment date; (ii) the effective date of an order under section 505(e) of the basic Act, other than clause (3) of the first sentence of such section 505(e), withdrawing or suspending the approval of such application.

(4) In the case of any drug which, on the day immediately preceding the enactment date, (A) was commercially used or sold inthe United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the amendments to section 201(p) made by this Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day.

1. Public Law 87–781, which was enacted October 10, 1962. The amendments made by such Public Law to the Federal Food, Drug, and Cosmetic Act included amendments establishing the requirement that new drugs be effective. Section 107(c) concerned the applicability of the amendments.

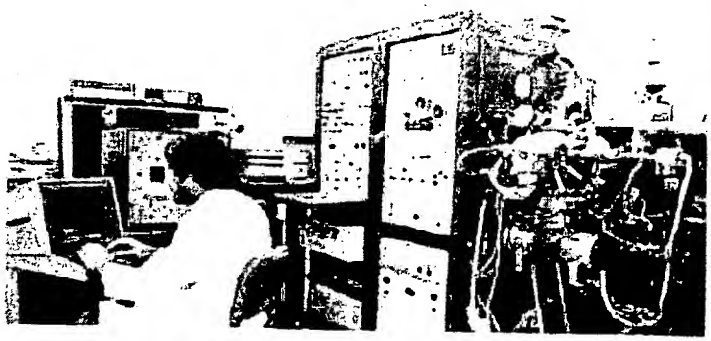
PUBLIC LAW 88–136; REVOLVING FUND

U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION

FDA Consumer
June 1981

The Story Of The Laws Behind The Labels

Part III
1962 Drug Amendments



Mass spectrometer used in an FDA laboratory

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I. 1906 Food and Drugs Act
II. 1938 Federal Food, Drug, and Cosmetic Act
III. 1962 Drug Amendments

1962 Drug Amendments

The trend toward preventive lawmaking continued. A drug tragedy in Europe, the births of thousands of deformed infants whose mothers had taken the new sedative thalidomide, focused public attention on pending U.S. legislation to further strengthen the Federal Food, Drug, and Cosmetic Act. The Drug Amendments of 1962, passed unanimously by the Congress, tightened control over prescription drugs, new drugs, and investigational drugs. It was recognized that no drug is truly safe unless it is also effective, and effectiveness was required to be established prior to marketing -- a milestone advance in medical history. Drug firms were required to send adverse reaction reports to FDA, and drug advertising in medical journals was required to provide complete information to the doctor -- the risks as well as the benefits. In the years since 1962 literally thousands of prescription drug items have been taken off the U.S. market because they lacked evidence of safety and/or effectiveness, or they have had their labeling changed to reflect

the known medical facts.

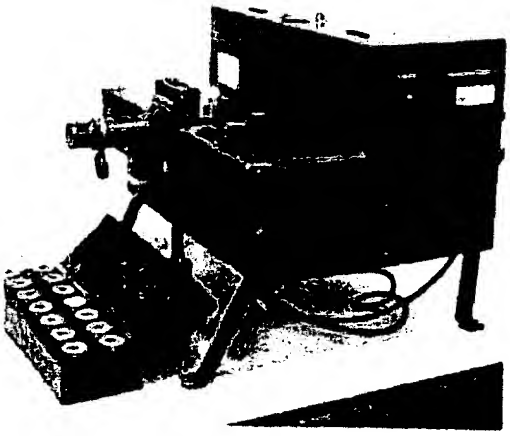
Preventing harm again was the goal of amendments passed in 1976, to insure safety and effectiveness of medical devices. Federal authority to regulate therapeutic devices was first provided in the FDC Act of 1938. As a result, hundreds of quack machines and gadgets were taken off the market. The growth of medical technology, however, soon made the 1938 act obsolete in regard to legitimate devices. Spectacular growth also occurred in the related field of medical diagnostic aids. Anticipating the need for better regulation in both areas, and FDA Bureau of Medical Devices and Diagnostic Products was officially created in February 1974. Years of study and many drafts of proposed laws developed by FDA and Congressional staff workers and industry experts culminated in the Medical Device Amendments of 1976, signed by President Gerald Ford on May 28. To avoid excess regulation the new law provides for classification of devices for controls appropriate for each class. Critically important devices, such as heart pacemakers or surgical implants, must be proved safe and effective before they can be marketed.

Preventing harm is again the purpose of the newest amendment of the basic Food, Drug, and Cosmetic Act, the Infant Formula Act of 1980, drafted by Congress to insure minimum amounts of essential nutrients in commercially prepared baby foods, and to establish safety and quality standards for such foods. The Congressional action followed reports during 1979 that over 100 infants had been made seriously ill because of the lack of chlorides in two soy-based formulas. The new law authorizes FDA to adjust nutritional standards for such foods to conform with the best available scientific knowledge. Manufacturers are required to periodically test their products and report promptly to FDA when they do not meet the official specifications.

Major Trends and Developments

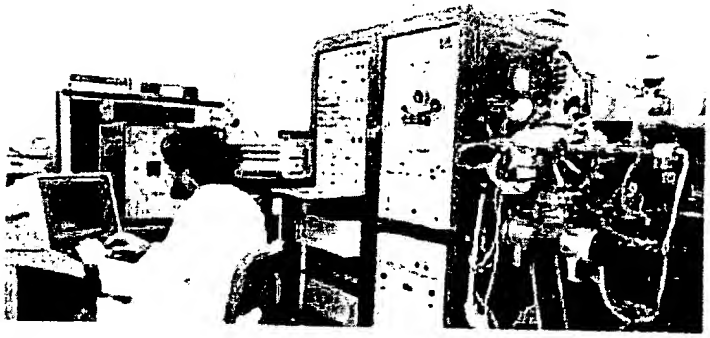
At the start of the 1950's the resources of FDA were seriously deficient. Appropriations and staff, never adequate, remained at approximately the levels prevailing in 1938 when Congress passed the present basic Federal Food, Drug, and Cosmetic Act, greatly increasing the Agency's responsibilities. In 1954, Commissioner Charles W. Crawford won approval by Nelson Rockefeller, undersecretary of the department, for the appointment of a representative Citizens Advisory Committee on the FDA, to study the adequacy of enforcement. The committee, adopting recommendations drafted by a distinguished industry lawyer, Charles Wesley Dunn, recommended a three-to fourfold increase in funds, to be accomplished in 5 to 10 years. The budget makers and the Congress were impressed by the committee's report, and a spectacular increase in FDA appropriations has since occurred -- from a $5 million budget in 1955 to over $320 million in 1980, with a staff increase from less than 1,000 to over 7,000.

Equally striking in the last quarter century has been the increase in FDA's scientific capability to detect and measure substances in foods, drugs, and cosmetics. FDA scientists, always outstanding for their skill in analytical chemistry, developed a new arsenal of spectrographic and chromatographic techniques, whereby contaminants can be measured in parts per billion or even per trillion. Today automated instruments can even print out the results of sample analyses in minutes, a procedure which once would have required weeks of laboratory benchwork. The increase in sensitivity of methods, by roughly one million times, revolutionized food and drug regulation. It is in this context that scientists must now decide such questions as where to draw the dividing line between consumer risk and benefits.



Visual spectrophotometer, developed in the early 1930's by FDA chemist Paul A. Clifford and physicist Brooks Brice, was the forerunner of equipment which has increased the sensitivity of FDA analytical methods approximately a million fold -- the difference between 10 parts in a million in the 1940's and less than one part per billion today.

The continuing revolution in analytical techniques is typified by this high-resolution, double-focusing mass spectrometer in the FDA Washington headquarters laboratories. This advanced unit is used to identify food toxicants ranging down to one part per billion.



Programs Transferred

From its beginning, FDA's mission has been consumer protection. As a consequence the Agency has initiated several major consumer protection programs now administered by other agencies, and today includes consumer programs transferred to FDA from other agencies.

A great chapter in FDA history came to an end in 1968 when the FDA Bureau of Drug Abuse Control was merged with Federal narcotic law enforcement in the Department of Justice. On it own initiative FDA has pioneered in the 1940's the Federal effort to curb abuse of nonnarcotic drugs, by prosecuting dealers who sold barbiturates and amphetamines without prescriptions. The advent of the dangerous hallucinogenic drug LSD in the 1960's magnified the problem. Working with inadequate law, unarmed, and with little experience in criminal investigation, FDA inspectors went undercover as drug peddlers and secured the conviction of hundreds of racketeers and pushers. When stronger drug abuse control amendments were passed in 1965, a new FDA Bureau of Drug Abuse Control was established, with a nationwide field service and over 300 trained agents. Anticipating ultimate consolidation with the Federal Bureau of Narcotics, FDA Commissioner George Larrick planned the new bureau as a separate establishment. With the transfer, FDA lost many experienced employees, and criminal investigation became a relatively minor field of activity.

Safety of household chemical products, appliances, toys, and other consumer goods is another area of consumer protection pioneered by FDA. The Caustic Poison Act, lobbied through Congress in 1927 by Dr. Chevalier Jackson and the American Medical Association, required labels to warn parents and protect children from accidental injury and death caused by lye and 10 other caustic chemicals. In 1960 thousands of other chemical products for home use came under FDA control when the Hazardous Substances Labeling Act was passed with strong industry support. To administer this law and subsequent amendments which expanded it, FDA developed an effective consumer safety program. With the passage of the Consumer Product Safety Act, in 1972, the FDA Bureau of Product Safety became the operating organization of a new independent Consumer Product Safety Commission.

Programs Added

Important health programs were merged with FDA as a result of a 1968 departmental reorganization. By transfer from the Publish Health Service, FDA became responsible for activities to:

- Assure safe milk supplies through cooperation with State and municipal milk control authorities;
- Assure that shellfish are harvested from unpolluted waters and handled in a sanitary manner;
- Assure safe food, water, and good sanitary facilities for travelers on trains, planes, ships, buses, and the interstate highways;
- Promote sanitary practices in restaurants and other food service facilities;
- Protect victims of accidental poisoning by providing poison control centers with information needed for emergency treatment.

The health hazards of radiation have been known since the discovery of radium and the x-ray. Before World War I, FDA was taking action against quack drugs and devices claimed to be radioactive -- some of them highly dangerous. About 1913 the Public Health Services became concerned with workers who contracted cancer from luminous paint they applied to watch dials. Overdosage with diagnostic x-rays increased greatly, becoming a major public health problem. Following World War II both PHS and FDA were involved in monitoring contamination of food, milk, and public water supplies due to radioactive fallout from open testing of atomic weapons. Meanwhile, electronic technology developed a host of new products -- television, microwave ovens, lasers, etc., which could emit harmful radiation. In 1968 a comprehensive Radiation Health and Safety Act was passed, and in 1971 the product-related activities of the PHS Bureau of Radiological Health were transferred to FDA, while its environmental activities were shifted to a new Environmental Protection Administration.

One more important health program was assigned to FDA in July 1972, from the National Institutes of Health -- the regulation of biological drugs. This, the oldest continuing Federal drug control program, was begun in 1902 to insure the safety and effectiveness of vaccines, serums, antitoxins, etc., by setting standards and licensing both the producers and their products. The transfer immediately strengthened control by applying provisions of the Federal Food, Drug, and Cosmetic Act as well as the licensing controls previously in effect. More effective regulation of blood banks has been a major accomplishment of FDA's new Bureau of Biologics.

From its beginning, the law defined food and drugs as products "for man and other animals." But livestock feed and veterinary drugs were left largely to State regulation until World War I made it important to increase food production. One way was to crack down on quack veterinary medicines, especially the numerous "cures" for hog cholera. For years the Bureau of Chemistry and FDA waged war against such products, saving farmers uncounted millions in livestock losses as well as the cost of worthless drugs. Today the law for animal products closely parallels the regulation of products for humans, and FDA's Bureau of Veterinary Medicine is as much involved with the health of human consumers of animal products as it is with the animals which produce them.

The Trend Toward Prevention

There are many ways to write FDA's history. It can be a story of the laws which Congress enacted, a story of famous cases to enforce those laws, a story of the organization and the people who built it, or a story about the changing technology and the scientific controversies, some settled, others still unsolved. And it can be all of these, but not in a few pages.

If there is one dominating theme it is the change from a law that was primarily a criminal statute, protecting consumers through the deterrent effect of court proceedings to a law that is now dominantly preventive through informative regulations and premarket controls.

The premarket approval laws made important changes in FDA's methods of control. They specifically required the Agency to issue regulations explaining the requirements and procedures. The 1962 Drug Amendments called for Current Good Manufacturing Practice Regulations to set standards for plant facilities, maintenance, laboratory controls, etc., to prevent errors or accidents which could harm consumers. The idea was too good to be restricted to drugs, and in 1969 the first

GMP's for food establishments were issued. All such regulations are based on actual industry practices. Today FDA inspectors especially look for GMP violations, as well as product violations.

The American public has little knowledge of the routine work of FDA, important as it is to every consumer. Much better known are its efforts to deal with newsmaking scientific problems. A succession of these, beginning with the cranberry recall of 1959, has greatly affected the Agency's work as well as its public image.

Those who read the papers or watch TV know FDA in terms of such topics as cyclamate in soft drinks, the food color Red No. 2, saccharin, nitrite, and caffeine. Chemicals and cancer are the great public health concerns of today. Much more is known about such matters than just 20 years ago, yet uncertainty about the risk of borderline carcinogens continues to hamper decisions. Generally a great deal of money is involved -- both for the users and the regulators who must seek scientifically valid answers. At the same time an inflexible law (the Delaney Clause) leaves little room for the exercise of judgment.

Fortunately, the regular business of consumer protection goes on as usual. Millions of times a day people in factories, warehouses, drugstores, and hospitals do things to comply with the food and drug law -- yet never give it a thought! Consumer protection happens because so many people do things the right way.

See also The Long Struggle for the 1906 Law.

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Guidance for FDA Staff and Industry

Marketed Unapproved Drugs — Compliance Policy Guide

Sec. 440.100
Marketed New Drugs Without Approved NDAs or ANDAs

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
June 2006

Compliance

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Contains Nonbinding Recommendations

Guidance for FDA Staff and Industry[1]

Marketed Unapproved Drugs — Compliance Policy Guide
Chapter - 4
Subchapter - 440

Sec. 440.100 Marketed New Drugs Without Approved NDAs or ANDAs

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This compliance policy guide (CPG) describes how we intend to exercise our enforcement discretion with regard to drugs marketed in the United States that do not have required FDA approval for marketing. This CPG supersedes section 440.100, Marketed New Drugs Without Approved NDAs or ANDAs (CPG 7132c.02). It applies to any drug required to have FDA approval for marketing, including new drugs covered by the Over-the-Counter (OTC) Drug Review, except for licensed biologics and veterinary drugs.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Reason for This Guidance

For historical reasons, some drugs are available in the United States that lack required FDA approval for marketing. A brief, informal summary description of the various categories of these drugs and their regulatory status is provided in Appendix A as general background for this document. The manufacturers of these drugs have not received FDA approval to legally market

[1] This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

their drugs, nor are the drugs being marketed in accordance with the OTC drug review. The new drug approval and OTC drug monograph processes play an essential role in ensuring that all drugs are both safe and effective for their intended uses. Manufacturers of drugs that lack required approval, including those that are not marketed in accordance with an OTC drug monograph, have not provided FDA with evidence demonstrating that their products are safe and effective, and so we have an interest in taking steps to either encourage the manufacturers of these products to obtain the required evidence and comply with the approval provisions of the Federal Food, Drug, and Cosmetic Act (the Act) or remove the products from the market. We want to achieve these goals without adversely affecting public health, imposing undue burdens on consumers, or unnecessarily disrupting the market.

The goals of this guidance are to (1) clarify for FDA personnel and the regulated industry how we intend to exercise our enforcement discretion regarding unapproved drugs and (2) emphasize that illegally marketed drugs must obtain FDA approval.

B. Historical Enforcement Approach

FDA estimates that, in the United States today, perhaps as many as several thousand drug products are marketed illegally without required FDA approval.[2] Because we do not have complete data on illegally marketed products, and because the universe of such products is constantly changing as products enter and leave the market, we first have to identify illegally marketed products before we can contemplate enforcement action. Once an illegally marketed product is identified, taking enforcement action against the product would typically involve one or more of the following: requesting voluntary compliance; providing notice of action in a *Federal Register* notice; issuing an untitled letter; issuing a Warning Letter; or initiating a seizure, injunction, or other proceeding. Each of these actions is time-consuming and resource intensive. Recognizing that we are unable to take action immediately against all of these illegally marketed products and that we need to make the best use of scarce Agency resources, we have had to prioritize our enforcement efforts and exercise enforcement discretion with regard to products that remain on the market.

In general, in recent years, FDA has employed a risk-based enforcement approach with respect to marketed unapproved drugs. This approach includes efforts to identify illegally marketed drugs, prioritization of those drugs according to potential public health concerns or other impacts on the public health, and subsequent regulatory follow-up. Some of the specific actions the Agency has taken have been precipitated by evidence of safety or effectiveness problems that has either come to our attention during inspections or been brought to our attention by outside sources.

III. FDA'S ENFORCEMENT POLICY

In the discussion that follows, we intend to clarify our approach to prioritizing our enforcement actions and exercising our enforcement discretion with regard to the universe of unapproved, illegally marketed drug products in all categories.

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[2] This rough estimate comprises several hundred drugs (different active ingredients) in various strengths, combinations, and dosage forms from multiple distributors and repackagers.

A. Enforcement Priorities

Consistent with our risk-based approach to the regulation of pharmaceuticals, FDA intends to continue its current policy of giving higher priority to enforcement actions involving unapproved drug products in the following categories:

Drugs with potential safety risks. Removing potentially unsafe drugs protects the public from direct and indirect health threats.

Drugs that lack evidence of effectiveness. Removing ineffective drugs protects the public from using these products in lieu of effective treatments. Depending on the indication, some ineffective products would, of course, pose safety risks as well.

Health fraud drugs. FDA defines health fraud as "[t]he deceptive promotion, advertisement, distribution or sale of articles . . . that are represented as being effective to diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a beneficial effect on health, but which have not been scientifically proven safe and effective for such purposes. Such practices may be deliberate or done without adequate knowledge or understanding of the article" (CPG Sec. 120.500). Of highest priority in this area are drugs that present a direct risk to health. Indirect health hazards exist if, as a result of reliance on the product, the consumer is likely to delay or discontinue appropriate medical treatment. Indirect health hazards will be evaluated for enforcement action based on section 120.500, Health Fraud - Factors in Considering Regulatory Action (CPG 7150.10). FDA's health fraud CPG outlines priorities for evaluating regulatory actions against indirect health hazard products, such as whether the therapeutic claims are significant, whether there are any scientific data to support the safety and effectiveness of the product, and the degree of vulnerability of the prospective user group (CPG Sec. 120.500).

Drugs that present direct challenges to the new drug approval and OTC drug monograph systems. The drug approval and OTC drug monograph systems are designed to avoid the risks associated with potentially unsafe, ineffective, and fraudulent drugs. The drugs described in the preceding three categories present direct challenges to these systems, as do unapproved drugs that directly compete with an approved drug, such as when a company obtains approval of a new drug application (NDA) for a product that other companies are marketing without approval (*see* section III.C., Special Circumstances – Newly Approved Product). Also included are drugs marketed in violation of a final and effective OTC drug monograph. Targeting drugs that challenge the drug approval or OTC drug monograph systems buttresses the integrity of these systems and makes it more likely that firms will comply with the new drug approval and monograph requirements, which benefits the public health.

Unapproved new drugs that are also violative of the Act in other ways. The Agency also intends, in circumstances that it considers appropriate, to continue its policy of enforcing the preapproval requirements of the Act against a drug or firm that also violates another provision of the Act, even if there are other unapproved versions of the drug

made by other firms on the market. For instance, if a firm that sells an unapproved new drug also violates current good manufacturing practice (CGMP) regulations, the Agency is not inclined to limit an enforcement action in that instance to the CGMP violations. Rather, the Agency may initiate a regulatory action that targets both the CGMP violation *and* the violation of section 505 of the Act (21 U.S.C. 355). This policy efficiently preserves scarce Agency resources by allowing the Agency to pursue all applicable charges against a drug and/or a firm and avoiding duplicative action. *See United States v. Sage Pharmaceuticals, Inc.*, 210 F.3d 475, 479-80 (5th Cir. 2000).

Drugs that are reformulated to evade an FDA enforcement action. The Agency is also aware of instances in which companies that anticipate an FDA enforcement action against a specific type or formulation of an unapproved product have made formulation changes to evade that action, but have not brought the product into compliance with the law. Companies should be aware that the Agency is not inclined to exercise its enforcement discretion with regard to such products. Factors that the Agency may consider in determining whether to bring action against the reformulated products include, but are not limited to, the timing of the change, the addition of an ingredient without adequate scientific justification (*see, e.g.*, 21 CFR 300.50 and 330.10(a)(4)(iv)), the creation of a new combination that has not previously been marketed, and the claims made for the new product.

B. Notice of Enforcement Action and Continued Marketing of Unapproved Drugs

FDA is not required to, and generally does not intend to, give special notice that a drug product may be subject to enforcement action, unless FDA determines that notice is necessary or appropriate to protect the public health.[3] The issuance of this guidance is intended to provide notice that any product that is being marketed illegally is subject to FDA enforcement action at any time.[4] The only exception to this policy is, as set forth elsewhere, that generally products subject to an ongoing DESI[5] proceeding or ongoing OTC drug monograph proceeding (i.e., an OTC product that is part of the OTC drug review for which an effective final monograph is not yet in place) may remain on the market during the pendency of

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[3] For example, in 1997, FDA issued a *Federal Register* notice declaring all orally administered levothyroxine sodium products to be new drugs and requiring manufacturers to obtain approved new drug applications (62 FR 43535, August 14, 1997). Nevertheless, FDA gave manufacturers 3 years (later extended to 4 (65 FR 24488, April 26, 2000)) to obtain approved applications and allowed continued marketing without approved new drug applications because FDA found that levothyroxine sodium products were medically necessary to treat hypothyroidism and no alternative drug provided an adequate substitute.

[4] For example, FDA may take action at any time against a product that was originally marketed before 1938, but that has been changed since 1938 in such a way as to lose its *grandfather* status (21 U.S.C. 321(p)).

[5] The Drug Efficacy Study Implementation (DESI) was the process used by FDA to evaluate for effectiveness for their labeled indications over 3,400 products that were approved only for safety between 1938 and 1962. DESI is explained more fully in the appendix to this document.

that proceeding[6] and any additional period specifically provided in the proceeding (such as a delay in the effective date of a final OTC drug monograph).[7] However, once the relevant DESI or OTC drug monograph proceeding is completed and any additional grace period specifically provided in the proceeding has expired, all products that are not in compliance with the conditions for marketing determined in that proceeding are subject to enforcement action at any time without further notice (*see, e.g.*, 21 CFR 310.6).

FDA intends to evaluate on a case-by-case basis whether justification exists to exercise enforcement discretion to allow continued marketing for some period of time after FDA determines that a product is being marketed illegally. In deciding whether to allow such a grace period,[8] we may consider the following factors: (1) the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of legally marketed products to meet the needs of patients taking the drug); (2) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application; (3) the burden on affected parties of immediately removing the products from the market; (4) the Agency's available enforcement resources; and (5) any special circumstances relevant to the particular case under consideration.

C. Special Circumstances — Newly Approved Product

Sometimes, a company may obtain approval of an NDA for a product that other companies are marketing without approval.[9] We want to encourage this type of voluntary compliance with the new drug requirements because it benefits the public health by increasing the assurance that marketed drug products are safe and effective — it also reduces the resources that FDA must expend on enforcement. Thus, because they present a direct challenge to the drug approval system, FDA is more likely to take enforcement action against remaining unapproved drugs in this kind of situation. However, we intend to take into account the circumstances once the product is approved in determining how to exercise our enforcement discretion with regard to the unapproved products. In exercising enforcement discretion, we intend to balance the need to provide incentives for voluntary compliance against the implications of enforcement actions on the marketplace and on consumers who are accustomed to using the marketed products.

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[6] OTC drugs covered by ongoing OTC drug monograph proceedings may remain on the market as provided in current enforcement policies. *See, e.g.*, CPG sections 450.200 and 450.300 and 21 CFR part 330. This document does not affect the current enforcement policies for such drugs.

[7] Sometimes, a final OTC drug monograph may have a delayed effective date or provide for a specific period of time for marketed drugs to come into compliance with the monograph. At the end of that period, drugs that are not marketed in accordance with the monograph are subject to enforcement action and the exercise of enforcement discretion in the same way as any other drug discussed in this CPG.

[8] For purposes of this guidance, the terms *grace period* and *allow a grace period* refer to an exercise of enforcement discretion by the Agency (i.e., a period of time during which FDA, as a matter of discretion, elects not to initiate a regulatory action on the ground that an article is an unapproved new drug).

[9] These may be products that are the same as the approved product or somewhat different, such as products of different strength.

When a company obtains approval to market a product that other companies are marketing without approval, FDA normally intends to allow a grace period of roughly 1 year from the date of approval of the product before it will initiate enforcement action (e.g., seizure or injunction) against marketed unapproved products of the same type. However, the grace period provided is expected to vary from this baseline based upon the following factors: (1) the effects on the public health of proceeding immediately to remove the illegal products from the market (including whether the product is medically necessary and, if so, the ability of the holder of the approved application to meet the needs of patients taking the drug); (2) whether the effort to obtain approval was publicly disclosed;[10] (3) the difficulty associated with conducting any required studies, preparing and submitting applications, and obtaining approval of an application; (4) the burden on affected parties of removing the products from the market; (5) the Agency's available enforcement resources; and (6) any other special circumstances relevant to the particular case under consideration. To assist in an orderly transition to the approved product(s), in implementing a grace period, FDA may identify interim dates by which firms should first cease *manufacturing* unapproved forms of the drug product, and later cease *distributing* the unapproved product.

The length of any grace period and the nature of any enforcement action taken by FDA will be decided on a case-by-case basis. Companies should be aware that a Warning Letter may not be sent before initiation of enforcement action and should not expect any grace period that is granted to protect them from the need to leave the market for some period of time while obtaining approval. Companies marketing unapproved new drugs should also recognize that, while FDA normally intends to allow a grace period of roughly 1 year from the date of approval of an unapproved product before it will initiate enforcement action (e.g., seizure or injunction) against others who are marketing that unapproved product, it is possible that a substantially shorter grace period would be provided, depending on the individual facts and circumstances.[11]

The shorter the grace period, the more likely it is that the first company to obtain an approval will have a period of de facto market exclusivity before other products obtain approval. For example, if FDA provides a 1-year grace period before it takes action to remove unapproved competitors from the market, and it takes 2 years for a second application to be approved, the first approved product could have 1 year of market exclusivity before the onset of competition. If FDA provides for a shorter grace period, the period of effective exclusivity could be longer.

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[10] For example, at the Agency's discretion, we may provide for a shorter grace period if an applicant seeking approval of a product that other companies are marketing without approval agrees to publication, around the time it submits the approval application, of a *Federal Register* notice informing the public that the applicant has submitted that application. A shortened grace period may also be warranted if the fact of the application is widely known publicly because of applicant press releases or other public statements. Such a grace period may run from the time of approval or from the time the applicant has made the public aware of the submission, as the Agency deems appropriate.

[11] Firms are reminded that this CPG does not create any right to a grace period; the length of the grace period, if any, is solely at the discretion of the Agency. For instance, firms should not expect any grace period when the public health requires immediate removal of a product from the market, or when the Agency has given specific prior notice in the *Federal Register* or otherwise that a drug product requires FDA approval.

FDA hopes that this period of market exclusivity will provide an incentive to firms to be the first to obtain approval to market a previously unapproved drug.[12]

D. Regulatory Action Guidance

District offices are encouraged to refer to CDER for review (with copies of labeling) any unapproved drugs that appear to fall within the enforcement priorities in section III.A. Charges that may be brought against unapproved drugs include, but are not limited to, violations of 21 U.S.C. 355(a) and 352(f)(1) of the Act. Other charges may also apply based on, among others, violations of 21 U.S.C. 351(a)(2)(B) (CGMP), 352(a) (misbranding), or 352(o) (failure to register or list).

[12] The Agency understands that, under the Act, holders of NDAs must list patents claiming the approved drug product and that newly approved drug products may, in certain circumstances, be eligible for marketing exclusivity. Listed patents and marketing exclusivity may delay the approval of competitor products. If FDA believes that an NDA holder is manipulating these statutory protections to inappropriately delay competition, the Agency will provide relevant information on the matter to the Federal Trade Commission (FTC). In the past, FDA has provided information to the FTC regarding patent infringement lawsuits related to pending abbreviated new drug applications (ANDAs), citizen petitions, and scientific challenges to the approval of competitor drug products.

APPENDIX

BRIEF HISTORY OF FDA MARKETING APPROVAL REQUIREMENTS AND CATEGORIES OF DRUGS THAT LACK REQUIRED FDA APPROVAL[13]

Key events in the history of FDA's drug approval regulation and the categories of drugs affected by these events are described below.

A. 1938 and 1962 Legislation

The original Federal Food and Drugs Act of June 30, 1906, first brought drug regulation under federal law. That Act prohibited the sale of adulterated or misbranded drugs, but did not require that drugs be approved by FDA. In 1938, Congress passed the Federal Food, Drug, and Cosmetic Act (the Act), which required that new drugs be approved for safety. As discussed below, the active ingredients of many drugs currently on the market were first introduced, at least in some form, before 1938. Between 1938 and 1962, if a drug obtained approval, FDA considered drugs that were identical, related, or similar (IRS) to the approved drug to be covered by that approval, and allowed those IRS drugs to be marketed without independent approval. Many manufacturers also introduced drugs onto the market between 1938 and 1962 based on their own conclusion that the products were generally recognized as safe (GRAS) or based on an opinion from FDA that the products were not new drugs. Between 1938 and 1962, the Agency issued many such opinions, although all were formally revoked in 1968 (*see* 21 CFR 310.100).

B. DESI

In 1962, Congress amended the Act to require that a *new drug* also be proven effective, as well as safe, to obtain FDA approval. This amendment also required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that FDA had approved as *safe* between 1938 and 1962 through the new drug approval process.

FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety between 1938 and 1962. The NAS/NRC created 30 panels of 6 professionals each to conduct the review, which was broken down into specific drug categories. The NAS/NRC reports for these drug products were submitted to FDA in the late 1960s and early 1970s. The Agency reviewed and re-evaluated the findings of each panel and published its findings in *Federal Register* notices. FDA's administrative implementation of the NAS/NRC reports was called the Drug Efficacy Study Implementation (DESI). DESI covered the 3,400 products specifically reviewed by the NAS/NRCs as well as the even larger number of IRS products that entered the market without FDA approval.

Because DESI products were covered by approved (pre-1962) applications, the Agency concluded that, prior to removing products not found effective from the market, it would follow

[13] This brief history document should be viewed as a secondary source. To determine the regulatory status of a particular drug or category of drugs, the original source documents cited should be consulted.

procedures in the Act and regulations that apply when an approved new drug application is withdrawn:

- All initial DESI determinations are published in the *Federal Register* and, if the drug is found to be less than fully effective, there is an opportunity for a hearing.
- The Agency considers the basis of any hearing request and either grants the hearing or denies the hearing on summary judgment and publishes its final determination in the *Federal Register.*
- If FDA's final determination classifies the drug as effective for its labeled indications, as required by the Act, FDA still requires approved applications for continued marketing of the drug and all drugs IRS to it – NDA supplements for those drugs with NDAs approved for safety, or new ANDAs or NDAs, as appropriate, for IRS drugs. DESI-effective drugs that do not obtain approval of the required supplement, ANDA, or NDA are subject to enforcement action.
- If FDA's final determination classifies the drug as ineffective, the drug and those IRS to it can no longer be marketed and are subject to enforcement action.

1. Products Subject to Ongoing DESI Proceedings

Some unapproved marketed products are undergoing DESI reviews in which a final determination regarding efficacy has not yet been made. In addition to the products specifically reviewed by the NAS/NRC (i.e., those products approved for safety only between 1938 and 1962), this group includes unapproved products identical, related, or similar to those products specifically reviewed (*see* 21 CFR 310.6). In virtually all these proceedings, FDA has made an initial determination that the products lack substantial evidence of effectiveness, and the manufacturers have requested a hearing on that finding. It is the Agency's longstanding policy that products subject to an ongoing DESI proceeding may remain on the market during the pendency of the proceeding. *See, e.g., Upjohn Co. v. Finch*, 303 F. Supp. 241, 256-61 (W.D. Mich. 1969).[14]

2. Products Subject to Completed DESI Proceedings

Some unapproved marketed products are subject to already-completed DESI proceedings and lack required approved applications. This includes a number of products IRS to DESI products for which approval was withdrawn due to a lack of substantial evidence of effectiveness. This group also includes a number of products IRS to those DESI products for which FDA made a

[14] Products first marketed after a hearing notice is issued with a different formulation than those covered by the notice are not considered subject to the DESI proceeding. Rather, they need approval prior to marketing. Under longstanding Agency policies, a firm holding an NDA on a product for which a DESI hearing is pending must submit a supplement prior to reformulating that product. The changed formulation may not be marketed as a related product under the pending DESI proceeding; it is a new drug, and it must be approved for safety and efficacy before it can be legally marketed. *See, e.g.*, "Prescription Drugs Offered for Relief of Symptoms of Cough, Cold, or Allergy" (DESI 6514), 49 FR 153 (January 3, 1984) (Dimetane and Actifed); "Certain Drugs Containing Antibiotic, Corticosteroid, and Antifungal Components" (DESI 10826), 50 FR 15227 (April 17, 1985) (Mycolog). *See also* 21 U.S.C. 356a(c)(2)(A). Similarly, firms without NDAs cannot market new formulations of a drug without first getting approval of an NDA.

final determination that the product is effective, but applications for the IRS products have not been both submitted and approved as required under the statute and longstanding enforcement policy (*see* 21 CFR 310.6). FDA considers all products described in this paragraph to be marketed illegally.

C. Prescription Drug Wrap-Up

As mentioned above, many drugs came onto the market before 1962 without FDA approvals. Of these, many claimed to have been marketed prior to 1938 or to be IRS to such a drug. Drugs that did not have pre-1962 approvals and were not IRS to drugs with pre-1962 approvals were not subject to DESI. For a period of time, FDA did not take action against these drugs and did not take action against new unapproved drugs that were IRS to these pre-1962 drugs that entered the market without approval.

Beginning in 1983, it was discovered that one drug that was IRS to a pre-1962 drug, a high potency Vitamin E intravenous injection named E-Ferol, was associated with adverse reactions in about 100 premature infants, 40 of whom died. In November of 1984, in response to this, a congressional oversight committee issued a report to FDA expressing the committee's concern regarding the thousands of unapproved drug products in the marketplace.

In response to the E-Ferol tragedy, CDER assessed the number of pre-1962 non-DESI marketed drug products. To address those drug products, the Agency significantly revised and expanded CPG section 440.100 to cover all marketed unapproved prescription drugs, not just DESI products. The program for addressing these marketed unapproved drugs and certain others like them became known as the *Prescription Drug Wrap-Up*. Most of the Prescription Drug Wrap-Up drugs first entered the market before 1938, at least in some form. For the most part, the Agency had evaluated neither the safety nor the effectiveness of the drugs in the Prescription Drug Wrap-Up.

A drug that was subject to the Prescription Drug Wrap-Up is marketed illegally, unless the manufacturer of such a drug can establish that its drug is grandfathered or otherwise not a *new drug*.

Under the 1938 grandfather clause (*see* 21 U.S.C. 321(p)(1)), a drug product that was on the market prior to passage of the 1938 Act and which contained in its labeling the same representations concerning the conditions of use as it did prior to passage of that Act was not considered a *new drug* and therefore was exempt from the requirement of having an approved new drug application.

Under the 1962 grandfather clause, the Act exempts a drug from the effectiveness requirements if its composition and labeling has not changed since 1962 and if, on the day before the 1962 Amendments became effective, it was (a) used or sold commercially in the United States, (b) not a new drug as defined by the Act at that time, and (c) not covered by an effective application. *See* Pub. L. 87-781, section 107 (reprinted following 21 U.S.C.A. 321); *see also USV Pharmaceutical Corp. v. Weinberger*, 412 U.S. 655, 662-66 (1973).

The two grandfather clauses in the Act have been construed very narrowly by the courts. FDA believes that there are very few drugs on the market that are actually entitled to grandfather status because the drugs currently on the market likely differ from the previous versions in some respect, such as formulation, dosage or strength, dosage form, route of administration, indications, or intended patient population. If a firm claims that its product is grandfathered, it is that firm's burden to prove that assertion. *See* 21 CFR 314.200(e)(5); *see also United States v. An Article of Drug (Bentex Ulcerine),* 469 F.2d 875, 878 (5th Cir. 1972); *United States v. Articles of Drug Consisting of the Following: 5,906 Boxes*, 745 F.2d 105, 113 (1st Cir 1984).

Finally, a product would not be considered a *new drug* if it is generally recognized as safe and effective (GRAS/GRAE) and has been used to a material extent and for a material time. *See* 21 U.S.C. 321(p)(1) and (2). As with the grandfather clauses, this has been construed very narrowly by the courts. *See, e.g., Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609 (1973); *United States v. 50 Boxes More or Less Etc.*, 909 F.2d 24, 27-28 (1st Cir. 1990); *United States v. 225 Cartons . . . Fiorinal*, 871 F.2d 409 (3rd Cir. 1989). *See also* Letter from Dennis E. Baker, Associate Commissioner for Regulatory Affairs, FDA, to Gary D. Dolch, Melvin Spigelman, and Jeffrey A. Staffa, Knoll Pharmaceutical Co. (April 26, 2001) (on file in FDA Docket No. 97N-0314/CP2) (finding that Synthroid, a levothyroxine sodium product, was not GRAS/GRAE).

As mentioned above, the Agency believes it is not likely that any currently marketed prescription drug product is grandfathered or is otherwise not a *new drug*. However, the Agency recognizes that it is at least theoretically possible. No part of this guidance, including the Appendix, is a finding as to the legal status of any particular drug product. In light of the strict standards governing exceptions to the approval process, it would be prudent for firms marketing unapproved products to carefully assess whether their products meet these standards.

D. New Unapproved Drugs

Some unapproved drugs were first marketed (or changed) after 1962. These drugs are on the market illegally. Some also may have already been the subject of a formal Agency finding that they are new drugs. *See, e.g.*, 21 CFR 310.502 (discussing, among other things, controlled/timed release dosage forms).

E. Over-the-Counter (OTC) Drug Review

Although OTC drugs were originally included in DESI, FDA eventually concluded that this was not an efficient use of resources. The Agency also was faced with resource challenges because it was receiving many applications for different OTC drugs for the same indications. Therefore, in 1972, the Agency implemented a process of reviewing OTC drugs through rulemaking by therapeutic classes (e.g., antacids, antiperspirants, cold remedies). This process involves convening an advisory panel for each therapeutic class to review data relating to claims and active ingredients. These panel reports are then published in the *Federal Register*, and after FDA review, tentative final monographs for the classes of drugs are published. The final step is the publication of a final monograph for each class, which sets forth the allowable claims, labeling, and active ingredients for OTC drugs in each class (*see, e.g.*, 21 CFR part 333). Drugs marketed in accordance with a final monograph are considered to be generally recognized as safe and effective (GRAS/GRAE) and do not require FDA approval of a marketing application.

Final monographs have been published for the majority of OTC drugs. Tentative final monographs are in place for virtually all categories of OTC drugs. FDA has also finalized a number of *negative monographs* that list therapeutic categories (*e.g.*, OTC daytime sedatives, 21 CFR 310.519) in which no OTC drugs can be marketed without approval. Finally, the Agency has promulgated a list of active ingredients that cannot be used in OTC drugs without approved applications because there are inadequate data to establish that they are GRAS/GRAE (*e.g.*, phenolphthalein in stimulant laxative products, 21 CFR 310.545(a)(12)(iv)(B)).

OTC drugs covered by ongoing OTC drug monograph proceedings may remain on the market as provided in current enforcement policies (*see, e.g.*, CPG sections 450.200 and 450.300, and 21 CFR part 330). This document does not affect the current enforcement policies for such drugs.

OTC drugs that need approval, either because their ingredients or claims are not within the scope of the OTC drug review or because they are not allowed under a final monograph or another final rule, are illegally marketed. For example, this group would include a product containing an ingredient determined to be ineffective for a particular indication or one that exceeds the dosage limit established in the monograph. Such products are new drugs that must be approved by FDA to be legally marketed.

Questions and Answers on the Unapproved Drug Compliance Policy Guide (CPG)

What action is FDA taking today?

FDA is issuing draft guidance designed to make sure that all drugs marketed in the U.S. have been shown to be safe and effective. For a variety of historical reasons, some drugs, mostly older products, continue to be marketed illegally in the United States. This guidance clearly articulates FDA's expectation that manufacturers of products requiring FDA approval show that their products are safe and effective. The draft guidance reflects the agency's desire to address this issue with policies that are predictable, reasonable, and supportive of the public health. The agency's approach encourages companies to comply with the drug approval process, but it also seeks to minimize disruption to the marketplace. The draft guidance explains that FDA will continue to give priority to enforcement actions involving unapproved drugs (1) with potential safety risks, (2) that lack evidence of effectiveness, and (3) that constitute health fraud. It also explains how the agency intends to address those situations in which a firm obtains FDA approval to sell a drug that other firms have long been selling without FDA approval.

Why is FDA taking action against unapproved drugs that people taking them believe are safe and effective?

A patient or prescriber may believe that a drug is safe or effective because of individual experience, but we have found that such subjective experiences can be misleading and insufficient to establish safety and effectiveness. Instead, we rely on carefully designed clinical trials that weigh the risks and benefits of taking a drug compared with the risks and benefits of taking a placebo or another accepted therapy. In many cases, we find that the original hypothesis that a drug is safe and effective is not correct. Carefully designed clinical trials have repeatedly demonstrated that the safety and effectiveness of drugs cannot be adequately established from anecdotal evidence or consumer or prescriber preferences. Our evidence-based system of drug approval provides great public health benefits to American consumers and health professionals because patients are able to rely on the medications that they take and avoid ineffective therapies or those for which the risks do not outweigh the benefits. They may also save money that they might otherwise spend on ineffective therapies or unsafe medicines. To support our evidence-based system of medicine, FDA must continue to take appropriate and judicious regulatory action against unapproved drugs. Such enforcement actions maintain the necessary incentives to develop and submit to FDA scientific evidence demonstrating the safety and effectiveness of marketed drug products as required by the Act and help preserve the integrity of the new drug approval system.

Why is FDA issuing this draft guidance?

FDA is issuing this draft guidance for reasons directly related to its mission of protecting and advancing the public health. This guidance clarifies what companies should do to obtain approval for their products, so that the products they market are proven to be safe and effective. The guidance is also designed to emphasize that illegally marketed drugs must obtain FDA approval. Moreover, FDA is explaining how it will exercise its "enforcement discretion" with respect to different types of illegally marketed drugs.

Will FDA consider the comments received on the draft guidance from interested parties?

Yes, FDA is inviting comments for 60 days and will closely consider them before finalizing the guidance.

Why now?

We believe the document is needed now because it has been almost 20 years since FDA last articulated its policies in this area, and because the law, regulations, and policies in this area are very complex. We believe that the complexity in this area of the law and policy, coupled with FDA's limited resources for enforcement in this area, has served to decrease some of the incentives needed to conduct the research needed to submit applications to FDA to prove drugs safe and effective. We believe that providing greater clarity and transparency will improve the public health and result in greater availability of drugs that have been proven to be both safe, effective, and of the highest quality.

How does this change FDA's approach?

The document does not represent a significant shift in FDA's approach. It is intended to explain existing and longstanding agency policies that may not have been explicitly articulated previously. As always, FDA will continue to give the highest priority to drugs with potential safety risks, drugs that lack evidence of effectiveness, and health fraud drugs.

What is articulated in this draft guidance document that was not explicit in the preexisting compliance policy guide?

The document discusses a scenario where a company has obtained an NDA for a product that other companies are marketing without approval and discusses how the agency might provide a "grace period" of enforcement discretion to phase out the marketing of the unapproved products. The draft guidance document states that FDA normally intends to allow a grace period of roughly one year before the agency begins enforcement actions. The guidance also identifies factors that could affect the length of the grace period.

Why has FDA allowed so many drugs to be sold without approval for so long?

A large number of drugs were being marketed before Congress made successive changes to the law that required drugs to be subject to FDA approval. Resource limitations have prevented FDA from determining the regulatory status of many drugs that may require approval and have prevented enforcement actions against many of the unapproved drugs

that have been determined to require approval. As always, FDA focuses its limited resources where they will do the most good, giving highest priority to drugs with potential safety risks, drugs that lack evidence of effectiveness, and health fraud drugs. In some cases, FDA action requiring application approvals must be very gradual to avoid shortages of medically necessary products, like levothyroxine.

If a drug has been illegally marketed for many years, is it exempt from FDA regulation?

No, FDA inaction would not change the legal status of a drug product.

If a drug has been marketed without FDA approval for many years with no known safety problems will FDA allow that drug to continue to be marketed indefinitely?

Manufacturers who sell illegally marketed unapproved drugs do so at the risk that FDA could take regulatory action at any time. An unapproved drug may come to the agency's attention for a variety of reasons that are discussed in the draft guidance document. The absence of "known" safety problems is not enough to meet the legally required standard of proving safety and effectiveness.

What is a "DESI" drug?

These are drugs that were approved solely on the basis of their safety prior to 1962. Thereafter, Congress required drugs to be shown to be effective as well. FDA initiated a Drug Efficacy Study Implementation (DESI) to evaluate the effectiveness of those drugs that had been previously approved on safety grounds alone. These drugs, and those identical, related, and similar to them, may continue to be marketed until the administrative proceedings evaluating their effectiveness have been concluded, at which point continued marketing is only permitted if an NDA is approved for such drugs. The vast majority of the DESI proceedings have been concluded, but a few are still pending.

Is a DESI drug just an old drug that exempt from FDA regulation?

No. DESI drugs are generally not the same as drugs marketed prior to 1938. DESI drugs include those that were the subject of pre-1962 FDA approvals and those drugs that are identical, related, and similar to them. These drugs are required to obtain approved applications after the DESI administrative proceedings have been concluded.

What is an "OTC monograph"?

An OTC monograph is a regulation that establishes the conditions (including claims, labeling, and active ingredients) under which a drug product for over-the-counter (OTC, or non-prescription) use may be recognized as generally recognized as safe and effective and not misbranded. Products marketed in accordance with final monographs do not require FDA-approved marketing applications.

Why did FDA issue a Federal Register notice and give manufacturers of levothyroxine sodium products 4 years to obtain approval of NDAs?

Levothyroxine sodium products were considered to be medically necessary products. Over

15 million Americans were taking these products when FDA determined that they were new drugs and required applications. The safety and effectiveness of these products had been well-established in the medical literature, but FDA had concerns about the quality of marketed products because of manufacturing issues. Patients can be at risk when the drug they are taking is not being manufactured properly or consistently from batch to batch. On the other hand, the public health consequences of immediately removing these products from the market would have far outweighed the risks of leaving them on the market for a reasonable period to allow companies to develop reliable formulations and obtain approval for them. There are now 8 manufacturers of approved levothyroxine sodium products on the market, and patients with thyroid deficiency now have much greater assurance the quality of the drugs they must take throughout their lives.

Is FDA required to publish a Federal Register notice before taking any action against any unapproved drug?

No. FDA may take action against unapproved new drugs without first publishing its intentions in the Federal Register. However, FDA will continue to be mindful of the effects of its action on consumers and health professionals and set its priorities according to their public health impact.

Has FDA considered a monograph system that would allow certain prescription drugs to be marketed without individual FDA approvals for each?

FDA is examining whether any class or classes of prescription drugs might be regulated under a monograph system in lieu of requiring individual applications. The Agency will be preparing a report to Congress, in the coming months, that considers the feasibility and cost of such a system. Although FDA has considered and declined this approach on several past occasions, the agency will consider whether new, relevant factors affect our analysis as we re-visit the question.

How does FDA intend to handle situations where there is an approved and unapproved version of the same drug?

In deciding whether, and in what manner, to take enforcement action against an unapproved drug, FDA will consider, among other factors, whether there is also an approved drug available to serve consumers who need the drug. Allowing continued marketing of unapproved drugs that compete against approved counterparts challenges the integrity of the drug approval system that is designed to avoid the risks associated with potentially unsafe and ineffective drugs. Allowing continued marketing of these drugs also undermines the incentives needed to conduct the scientific studies to determine the safety and effectiveness of drugs, which benefits the public health.

Should consumers and health professionals be worried that they will lose access to drugs they rely on?

FDA will continue to be mindful of the effects of any regulatory action on consumers and health professionals. The highest priority for enforcement action will continue to be drugs with potential safety risks, drugs that lack evidence of effectiveness, and health fraud drugs. Before pursuing regulatory action, FDA will consider the effects on the public health of

such action, including whether the product is medically necessary and, if so, the ability of legally marketed products to meet patient needs.

What drugs will FDA take off the market?

The highest priority for enforcement action will continue to be drugs with potential safety risks, drugs that lack evidence of effectiveness, and health fraud drugs. FDA will proceed on a case-by-case basis with these priorities in mind, without adversely affecting public health, imposing any undue burdens on consumers, or unnecessarily disrupting the market.

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